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## Analysis of NTP Rodent Cancer Bioassay Data

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### Outline of the Talk

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- Some motivating examples from NTP studies
- The new test statistic
- The null distribution
- Results from simulation studies
- Re-analysis of the NTP examples
- Conclusions

### NTP Example 1

#### Methyleugenol (Male Rats)

- Tumor: Skin Fibroma
- Dose (mg/Kg): 0 37 75 150
- Number of tumors: 1 9 8 5
- Poly-3 tumor rates: .02 .22 .21 .15
- P-value (NTP Poly-3 trend test): 0.11

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### NTP Example 2

#### Isoprene (Female Rats)

- Tumor: Mammary Gland Fibroadenoma
- Dose (ppm): 0 220 700 7000
- Number of tumors: 19 35 32 32
- Poly-3 tumor rates: .43 .74 .74 .73
- P-value (NTP Poly-3 trend test): 0.11

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### NTP Example 3

#### Chloroprene (Female rats)

- Tumor: Alveolar/Bronchiolar Adenoma
- Dose (ppm): 0 12.8 32 82
- Number of tumors: 1 0 0 3
- Poly-3 tumor rates: .024 0 0 .074
- P-value (NTP Poly-3 trend test): 0.06

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### Motivation for the New Trend Test

- The NTP trend test generally performs well when the trend is linear. However, it loses power as the pattern of response deviates from linearity.
- This motivates the new trend test which is almost as good as NTP's trend test for linear response and often performs significantly better for non-linear patterns.

### Poly-3 Isotonic Regression Test

Peddada, Dinse and Haseman (2005, *JRSS-C*, to appear)

Related articles:

Peddada, Prescott and Conaway (2001, *Biometrics*)  
Hwang and Peddada (1994, *Annals of Statistics*)

### Some Notations

Let  $n_i^*$  denote the Poly - 3 adjusted sample size.

$$\hat{\pi}_i = \frac{Y_i}{n_i}, \quad i = 1, 2, \dots, k.$$

$$\tilde{\pi}_1 = \min_i \left( \frac{\sum_{j=1}^i n_j^* \hat{\pi}_j}{\sum_{j=1}^i n_j^*} \right), \quad \tilde{\pi}_k = \max_i \left( \frac{\sum_{j=i}^k n_j^* \hat{\pi}_j}{\sum_{j=i}^k n_j^*} \right),$$

(Pool Adjacent Violator Algorithm, PAVA)

### Poly-3 Isotonic Regression Test

For  $j^{th}$  animal in the  $i^{th}$  dose group, let

$$r_{ij} = Y_{ij} - \frac{\sum_j Y_{ij}}{\sum_j n_i} w_{ij}, \quad \bar{r}_i = \sum_j r_{ij}, \quad N = \sum_i n_i,$$

$$S^2 = \frac{\sum_j (r_{ij} - \bar{r}_i)^2}{N - k}, \quad w_{ij} \text{ is the associated Poly - 3 weight.}$$

Define

$$W_1 = \frac{\tilde{\pi}_k - \tilde{\pi}_1}{S \sqrt{\frac{n_1}{n_1^2} + \frac{n_k}{n_k^2}}}$$

### Poly-3 Isotonic Regression Test

- Denote the NTP's trend test statistic by

$$W_2 = g(\hat{\pi}_1, \hat{\pi}_2, \dots, \hat{\pi}_k)$$

- Then the proposed test statistic is

$$W = \max(W_1, W_2)$$

### The null distribution of $W$

- For  $i = 1, 2, \dots, k$ , let  $Z_i \stackrel{ind}{\sim} N(0,1)$

- Denote

$$\hat{Z}_i = \max_{1 \leq t \leq i} \min_{t \leq j \leq k} \frac{\sum_{j=t}^k Z_j}{t - s + 1}$$

- Then

$$W \stackrel{approximately}{\sim} \max \left( \frac{\hat{Z}_k - \hat{Z}_1}{\sqrt{2}}, g(Z_1, Z_2, \dots, Z_k) \right)$$

### Comparison between *W* and NTP Poly-3 trend test : Simulation experiments

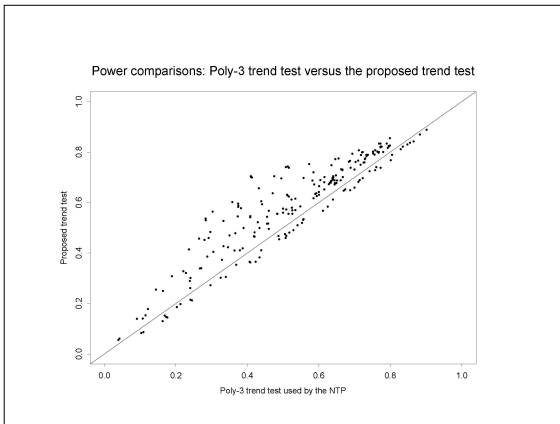
- As in Bailer and Portier (1988), Dinse (1994), etc. simulations were performed under Weibull models for incidence and mortality.
- 600 different non-null configurations and 120 different null configurations were considered.
  - tumor incidence ratios (6 different patterns)
  - background rates (4 different patterns)
  - mortality rates (5 different patterns)
  - tumor onset shape parameters (3 patterns: 1.5, 3, 6)
  - dose patterns (2 patterns: 2-fold and 5-fold spacing)

### False Positive Rate (Type I Error Rate)

No significant difference in the false positive rate between the two test procedures

### Sensitivity (Power)

- Results for 2-fold dose spacing are summarized in the attached plot.
- Points above the diagonal correspond to the case where the proposed test is significantly better than NTP's Poly-3 trend test.
- Points below the diagonal correspond to the case where the NTP's Poly-3 trend test is significantly better than the proposed trend test.




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### Conclusions based on the Simulation Studies

- The proposed test enjoys larger power than NTP Poly-3 trend test in most situations.
  - Gains in power can be substantial:
    - in the best case it is 28% (for NTP Poly-3 trend test) versus 53% (for the proposed trend test).
  - Loss in power is minimal:
    - in the worst case it is 11% (for NTP Poly-3 trend test) versus 8% (for the proposed trend test).

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### Back to Example 1

#### Methyleugenol (Male Rats)

Tumor: Skin Fibroma

Number of tumors: 1, 9, 8, 5

- P-value (NTP Poly-3 trend test): 0.110
- P-value (Proposed trend test): 0.027
- NTP's conclusion: Neoplastic effect

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- Tumor: Mammary Gland Fibroadenoma  
Number of tumors: 19, 35, 32, 32

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- Tumor: Alveolar/Bronchiolar Adenoma  
Number of tumors: 1, 0, 0, 3

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